

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year)
 02 July 2001 (02.07.01)

International application No.
 PCT/US00/24962

Applicant's or agent's file reference
 HMR2023

International filing date (day/month/year)
 13 September 2000 (13.09.00)

Priority date (day/month/year)
 14 September 1999 (14.09.99)

Applicant

FINK, David, M. et al

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

12 April 2001 (12.04.01)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Juan Cruz

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | | |
|--|---|--|---|
| Applicant's or agent's file reference HMR2023 | FOR FURTHER ACTION | | see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. |
| International application No. PCT/US 00/24962 | International filing date (day/month/year) 13/09/2000 | (Earliest) Priority Date (day/month/year) 14/09/1999 | |
| Applicant AVENTIS PHARMACEUTICALS, INC. et al. | | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT 00/24962

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D498/04 C07D519/00 A61K31/40 A61K31/55 A61K31/501
 A61K31/42 A61K31/44 A61K31/506 A61P25/18
 //(C07D498/04,333:00,261:00),(C07D519/00,498:00,451:00),

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| A | EP 0 221 414 A (HOECHST-ROUSSEL PHARMACEUTICALS INC.) 13 May 1987 (1987-05-13) the whole document | 1-120, 123-139 |
| X | examples 5,14,41 ---- | 121 |
| A | WO 99 40067 A (DUPHAR INTERNATIONAL RESEARCH B.V.) 12 August 1999 (1999-08-12) the whole document ----- | 1-139 |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

14 February 2001

Date of mailing of the international search report

21/02/2001

Name and mailing address of the ISA

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 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Beslier, L

INTERNATIONAL SEARCH REPORT

International Application No

PCT 00/24962

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 (C07D519/00, 498:00, 495:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| | | |

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Further documents are listed in the continuation of box C.

☒

Patent family members are listed in annex.

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A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

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NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Beslier, L

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT 00/24962

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| EP 221414 A | 13-05-1987 | US 4728651 A | 01-03-1988 |
| | | AU 6433786 A | 30-04-1987 |
| | | DK 507986 A | 25-04-1987 |
| | | HU 45061 A,B | 30-05-1988 |
| | | JP 62103086 A | 13-05-1987 |
| | | PT 83606 A,B | 01-11-1986 |
| | | US 4769472 A | 06-09-1988 |
| | | ZA 8608065 A | 24-06-1987 |
| WO 9940067 A | 12-08-1999 | AU 3327399 A | 23-08-1999 |
| | | EP 1054885 A | 29-11-2000 |

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| | | |
|---|---|---|
| Applicant's or agent's file reference HMR2023 | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | |
| International application No. PCT/US00/24962 | International filing date (day/month/year) 13/09/2000 | Priority date (day/month/year) 14/09/1999 |
| International Patent Classification (IPC) or national classification and IPC C07D498/04 | | |
| Applicant AVENTIS PHARMACEUTICALS, INC. et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

| | |
|---|---|
| Date of submission of the demand 12/04/2001 | Date of completion of this report 07.12.2001 |
| Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized officer Baston, E Telephone No. +49 89 2399 8229  |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/24962

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-136 as originally filed

Claims, No.:

1-117,127-139 as originally filed

118-126 as received on 25/10/2001 with letter of 25/10/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/24962

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 123,126-136 "with respect to industrial applicability".

because:

- ☒ the said international application, or the said claims Nos. 123,126-136 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|---------------------|------|--------|-------|
| Novelty (N) | Yes: | Claims | 1-139 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | 1-139 |

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/24962

| | | | |
|-------------------------------|------|--------|--------------------------|
| | No: | Claims | |
| Industrial applicability (IA) | Yes: | Claims | 1-122, 124, 125, 137-139 |
| | No: | Claims | |

2. Citations and explanations
see separate sheet

To section III

Claims 123 and 126-136 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

To section V

1.) The following documents were cited in the search report and were considered for the examination of the present application:

D1: EP-A-0 221 414 (HOECHST-ROUSSEL PHARMACEUTICALS INC.) 13 May 1987

D2: WO 99 40067 A (DUPHAR INTERNATIONAL RESEARCH B.V.) 12 August 1999

The present application is related to thienoisoxazolyl- and thienylpyrazolyl derivatives that are antagonists of the dopamine D4 receptor. These compounds are considered to be useful for the treatment of CNS diseases like obsessive compulsive disorder, schizophrenia or parkinson.

2.) D1 discloses related compounds for use as antihypertensive agents. Structures from this document, that would interfere with this application are excluded via proviso (claim 1, page 138, line 13-line 17: Q cannot be indolyl or phenyl).

Claims 1-120 (compounds), 121,122 (precursors), 124,125 (composition), 123,126-136 (methods of treatment) and 137-139 (methods of making compounds) are novel (Art. 33(2) PCT), since D1 and D2 (benzisoazole derivatives) differ strongly with respect to the claimed subject-matter.

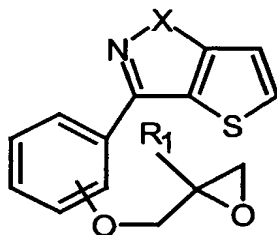
3.) Claims 1-139 involve an inventive step (Art. 33(3) PCT), since the presently claimed compounds are not suggested by any document of the prior art. Moreover the binding affinity for the dopamine D4 receptor is demonstrated for various examples along with suitable in vivo testings (MK-801 stereotypy in mice) for select congeners.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/24962

4.) For the assessment of the present claims 123 and 126-136 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

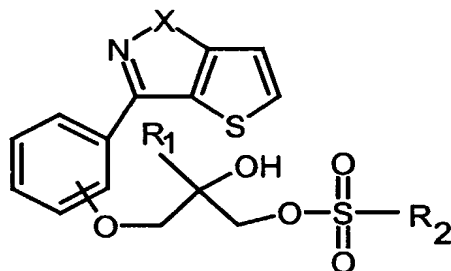
118. The compound of claim 117 which is (2R)-1-[(1H-benzimidazol-2-ylmethyl)amino]-3-[3-thieno[2,3-d]isoxazol-3-yl-phenoxy]propan-2-ol.
119. A compound according to claim 1, wherein R₃ is 1,2,3,4-tetrahydronaphthyl.
120. The compound of claim 119 which is (2R)-1-(1,2,3,4-tetrahydronaphthalen-1-ylamino)-3-[3-thieno[2,3-d]isoxazol-3-yl)phenoxy]propan-2-ol.
121. A compound of formula



wherein X is N(CH₃) or O; and

R₁ is H or C₁₋₆alkyl.

122. A compound of formula



wherein X is N(CH₃) or O;

R₁ is H or C₁₋₆alkyl; and

R₂ is CH₃, F, p-bromobenzene, p-nitrobenzene, or p-methylbenzene.

123. A method for antagonizing the effects of dopamine at the D₄ receptor comprising administering a compound according to claim 1 to a patient in need thereof.
124. A composition comprising a compound according to claim 1 in admixture with an inert carrier.
125. The composition according to claim 124 wherein said inert carrier is a pharmaceutical carrier.
126. A method of treating psychoses comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to claim 1.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/24962

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D498/04 C07D519/00 A61K31/40 A61K31/55 A61K31/501
A61K31/42 A61K31/44 A61K31/506 A61P25/18
//(C07D498/04, 333:00, 261:00), (C07D519/00, 498:00, 451:00),

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| A | EP 0 221 414 A (HOECHST-ROUSSEL PHARMACEUTICALS INC.) 13 May 1987 (1987-05-13) the whole document | 1-120, 123-139 |
| X | examples 5, 14, 41 | 121 |
| A | WO 99 40067 A (DUPHAR INTERNATIONAL RESEARCH B.V.) 12 August 1999 (1999-08-12) the whole document | 1-139 |

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
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X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

14 February 2001

Date of mailing of the international search report

21/02/2001

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

Authorized officer

Beslier, L

INTERNATIONAL SEARCH REPORT

Int. Application No.

PCT/ 00/24962

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 (C07D519/00, 498:00, 495:00)

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Fax: (+31-70) 340-3016

Authorized officer

Beslier, L

INTERNATIONAL SEARCH REPORT

Information on patent family members

In International Application No

P US 00/24962

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|----------------------------|---------------------|
| EP 221414 | A | 13-05-1987 | US 4728651 A | 01-03-1988 |
| | | | AU 6433786 A | 30-04-1987 |
| | | | DK 507986 A | 25-04-1987 |
| | | | HU 45061 A, B | 30-05-1988 |
| | | | JP 62103086 A | 13-05-1987 |
| | | | PT 83606 A, B | 01-11-1986 |
| | | | US 4769472 A | 06-09-1988 |
| | | | ZA 8608065 A | 24-06-1987 |
| WO 9940067 | A | 12-08-1999 | AU 3327399 A | 23-08-1999 |
| | | | EP 1054885 A | 29-11-2000 |